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| EXAMINER | |
|---|---|
| BUNNER, BRIDGET E | |
| **ART UNIT** | **PAPER NUMBER** |
| 1647 | |

DATE MAILED: 10/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/086,177 | TUDAN ET AL. | |
| | Examiner | Art Unit | |
| | Bridget E. Bunner | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *23 and 27-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23 and 27-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Application, Amendments and/or Claims*

The amendment of 25 July 2005 has been entered in full. Claims 23 and 27-29 are amended. Claims 1-22 and 24-26 are cancelled. Claims 30-32 are added.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 23 and 27-32 are under consideration in the instant application.

### *Withdrawn Objections and/or Rejections*

1. The objections to the specification at pg 3 of the previous Office Action (18 January 2005) are *withdrawn* in view of the amended specification and title (25 July 2005).

2. The objection to claim 28 at pg 3 of the previous Office Action (18 January 2005) is *withdrawn* in view of the amended claim (25 July 2005).

3. The rejections of claims 23-29 under 35 U.S.C. 112, second paragraph, as set forth at pg 9-10 of the previous Office Action (18 January 2005) are *withdrawn* in view of the amended and cancelled claims (25 July 2005).

4. The rejection of claim 23 and 25 under 35 U.S.C. 102(a) as set forth at pg 10-11 of the previous Office Action (18 January 2005) is *withdrawn* in view the amendment of claim 23 and the cancellation of claim 25 (25 July 2005).

### *Claim Objections*

5. Claim 28 is objected to because of the following informalities: Claim 28 depends from claims 24-26, which are currently cancelled. Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

***Scope of Enablement***

6. Claims 23 and 27-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a CXC chemokine receptor 4 (CXCR4) agonist peptide comprising (a) an N-terminal sequence comprising amino acids 1-14 of stromal cell derived factor-1 (SDF-1); (b) a C-terminal sequence comprising amino acid 55-67 of SDF-1 and wherein the C-termini is an acid or an amide; (c) a peptide spacer sequence linking the N-terminal sequence to the C-terminal sequence, wherein the peptide spacer sequence comprises 4 glycine residues; and optionally (d) an internal cyclic lactam bond between amino acid residues 20 and 24 in the C-terminal sequence of the peptide agonist wherein residue 24 is E or D, ***does not reasonably provide enablement*** for a CXC chemokine receptor 4 (CXCR4) agonist peptide comprising (a) a N-terminal sequence homologous to amino acids 1-14 of native SDF-1, the N-terminal sequence having the formula K[P or D]VS[L or D]SYR[C or A or F or H or W or Y]P[C or F or W or W or H or A]RFF; (b) a C-terminal sequence homologous to amino acids 55-67 of native SDF-1, the C-terminal sequence having the following formula wherein the residues that may form an internal cyclic amide bridge are identified by an *, L[K or O]*WIQ[ E or D]*YLE[K or O]*ALN, and (c) a spacer of the formula $G_{1-4}$ or $(CH_2)_{1-4}$. The basis for this rejection is set forth at pg 3-6 of the previous Office Action (18 January 2005).

Applicant's arguments (25 July 2005), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that to expedite prosecution, while maintaining that the present specification fully supports the original claims, the claimed have been amended so that they are

directed to the embodiments disclosed in Example 13. Applicant indicates that claim 23 has been amended, showing the specific alternative monomers at seven positions within the N-terminal and C-terminal regions as listed in the sequences set out in Example 13.

Applicant's arguments have been fully considered but are not found to be persuasive. As discussed in the previous Office Action of 18 January 2005, the specification does not teach all possible CXCR4 agonist peptides comprising (a) a N-terminal sequence *homologous* to amino acids 1-14 of native SDF-1 ; (b) a C-terminal sequence *homologous* to amino acids 55-67 of native SDF-1, the C-terminal sequence having an internal cyclic amide bridge; and (c) a spacer sequence linking the N-terminal sequence to the C-terminal sequence, wherein the spacer is of the formula $G_{1-4}$ of $(CH_2)_{1-4}$. Undue experimentation would be required of one skilled in the art to generate the infinite number of CXCR4 peptides recited in the claims and screen the same for activity. Although Applicant has amended claim 23, the claims are still interpreted by the Examiner as encompassing a large number of CXCR4 agonist peptides. For example, the claims recite specific N-terminal and C-terminal sequences of SDF-1 that have numerous possible mutations or variations, i.e. "[C or A or F or H or W or Y]" (see claim 23(a)). The claims also recite several different resides that form an internal cyclic amide bridge. The claims recite that the spacer may have one to four glycine residues or one to four of $CH_2$. The claims also recite numerous amino acid sequences (and SEQ ID NOs) and structures of agonist peptides with a PEG moiety attached. However, undue experimentation would be required of one skilled in the art to generate the infinite number of CXCR4 peptides recited in the claims and screen the same for activity. Furthermore, the specification of the instant application only discloses activities for

the following CXCR agonist peptides (see pages pg 52, lines 1-5, 20-25; Table 2; pg 56, lines 17-22; Figure 6; pg 55, lines 1-21; Table 4; Figures 7; 59, lines 1-7; Figures 10-11) :

(1) SDF-1(1-14)-$(G)_4$-SDF-1(55-67)-amide (also referred to as CTCE0017; SEQ ID NO: 15),

(2) SDF-1(1-14)-$(G)_4$-SDF-1(55-67)-K20/D24-cyclic amide (SEQ ID NO: 25),

(3) SDF-1(1-14)-$(G)_4$-SDF-1(55-67)-acid (also referred to as CTCE0013; SEQ ID NO: 13),

(4) and SDF-1(1-14)-$(G)_4$-SDF-1(55-67)-K20/E24-cyclic amide (referred to as CTCE0021; SEQ ID NO: 23).

The specification does not teach the generation and screening of any other agonist peptides other than the peptides listed above. The broad discussion of how to make and screen for CXCR4 agonists in the specification constitutes an invitation to experiment by trial and error. This is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For example, other than amino acids 1-14 of the N-terminal sequence of SDF-1 and amino acids 55-67 of the C-terminal sequence of SDF-1, there is little guidance in the specification indicating which amino acids from the N-terminal domain and which amino acids from the C-terminal domain of SDF-1 can be linked together to generate a functional agonist peptide. A large quantity of experimentation would also be required of the skilled artisan to generate an agonist peptide with one to four of $CH_2$ spacers and screen the same for activity. Additionally, one skilled in the art would not be able to predict the structure and function of the CXCR4 peptide when the peptide contains a spacer containing one to three glycine residues. Luo et al. (Biochem Biophys Res Comm 264 : 42-47, 1999) generated N-terminal and C-terminal SDF-1 peptides and teach that the use of the four glycine

linker "is to allow the N- and C-terminal fragments to adopt a spatial orientation similar to the native protein structure" (pg 43, col 2).

Regarding the numerous amino acid variations and combinations thereof recited in the claims, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may

not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

***Written Description***

7. Claims 23, 27-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed

invention. The basis for this rejection is set forth at pg 6-9 of the previous Office Action (18 January 2005).

Applicant's arguments (25 July 2005), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that to expedite prosecution, while maintaining that the present specification fully supports the original claims, the claimed have been amended so that they are directed to the embodiments disclosed in Example 13. Applicant indicates that claim 23 has been amended, showing the specific alternative monomers at seven positions within the N-terminal and C-terminal regions as listed in the sequences set out in Example 13.

Applicant's arguments have been fully considered but are not found to be persuasive. As discussed in the previous Office Action of 21 January 2005, to provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. The courts have specifically stated that the skilled artisan cannot envision the *detailed chemical structure* of an encompassed polypeptide until the structure is disclosed, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Applicant

has not described or shown possession of all polypeptides comprising (a) a N-terminal sequence *homologous* to amino acids 1-14 of native SDF-1 ; (b) a C-terminal sequence *homologous* to amino acids 55-67 of native SDF-1, the C-terminal sequence having an internal cyclic amide bridge; and (c) a spacer sequence linking the N-terminal sequence to the C-terminal sequence, wherein the spacer is of the formula $G_{1-4}$ of $(CH_2)_{1-4}$. Additionally, in this case, the only factors present in the claims are a partial structure in the form of an amino acid sequence with numerous variations, a requirement that the sequence be native, and a requirement that the peptide is an agonist. There is no identification of any particular portion of the structure that must be conserved in order to conserve the required function. In the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Clearly, such does not constitute disclosure of a representative number of examples of, nor adequate written description for, the claimed genus.

The broad brush discussion of making and screening for variants in the instant specification does not constitute a disclosure of a representative number of members. No such variants were made or shown to have activity. Only the CXCR4 agonist peptides referred to as CTCE0017 (SEQ ID NO: 15), the peptide of SEQ ID NO: 25, CTCE0013 (SEQ ID NO: 13), CTCE0021 (SEQ ID NO: 23) are disclosed. The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. Such does not constitute an adequate written description for the claimed variants. Additionally, no *native* SDF-1 sequence variants of CXCR4 agonist peptides have been disclosed. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483.

***New Matter***

8. Claims 23 are27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims are directed to a CXC chemokine receptor 4 (CXCR4) agonist peptide comprising (a) a N-terminal sequence homologous to amino acids 1-14 of native SDF-1, the N-terminal sequence having the formula K[P or D]VS[L or D]SYR[C or A or F or H or W or Y]P[C or F or W or W or H or A]RFF; (b) a C-terminal sequence homologous to amino acids 55-67 of native SDF-1, the C-terminal sequence having the following formula wherein the residues that may form an internal cyclic amide bridge are identified by an *, L[K or O]*WIQ[ E or D]*YLE[K or O]*ALN, and (c) a spacer of the formula $G_{1-4}$ or $(CH_2)_{1-4}$.

The specification as originally filed does not provide adequate written description for a spacer with the formula $(CH_2)_{1-4}$. It is not expressly asserted, nor does it flow naturally from the specification. In the response filed 25 July 2005, Applicant indicates that support for such linkers are found in paragraph 148. The Examiner assumes that Applicant is referencing paragraph 148 in US20030148940. It is noted that this correlates to page 46, lines 8-10 of the instant specification. However, the Examiner has interpreted this language as referring to the glycine spacer and not the $CH_2$ spacer now recited in the claims. The specification discloses that "[i]n some embodiments, $(CH_2)_n$ may for example be used as a linker between N- and C-terminal, where n is an integer and may for example be less than 20, 30, 40, 50, or 100" (pg 44,

lines 26-28). However, as indicated above, the specification as originally filed does not provide adequate written description for a spacer with the formula $(CH_2)_{1-4}$

***Conclusion***

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

BEB
Art Unit 1647
04 October 2005

ELIZABETH KEMMERER
PRIMARY EXAMINER